

In the claims

The following amendments are made with respect to the claims in the international application PCT/GB03/03803.

This listing of claims will replace all prior versions and listings of claims in this application.

1 (Original). A system for detecting a physical, chemical or biochemical reaction comprising:

a coherent radiation source for producing an incident wave;

a carrier surface for supporting a specimen to be analysed, the carrier surface mounted on a substrate and capable of supporting surface electromagnetic waves (SEW);

means for splitting the incident wave into an SEW and a first scattered wave, wherein the SEW propagates along the carrier surface and interacts with the specimen;

means for generating a second scattered wave from the SEW; and,

a detector for monitoring the interference between the first scattered wave and the second scattered wave.

2 (Currently amended). [[A]] The system according to claim 1, wherein the incident wave is a SEW.

3 (Currently amended). [[A]] The system according to claim 1 [[or 2]], wherein the means for splitting the incident wave, and/or generating the second scattered wave, is a discontinuity in the carrier surface.

4 (Cancelled).

5 (Currently amended). [[A]] The system according to claim 3 [[or 4]], wherein the discontinuity is a discontinuity in the thickness of the carrier surface.

6 (Currently amended). [[A]] The system according to claim 3 [[or 4]], wherein the discontinuity is a discontinuity in the refractive index of the carrier surface or adjacent materials.

7 (Currently amended). [[A]] The system according to ~~any preceding~~ claim 1, wherein the specimen is contained in a reaction vessel containing a reaction fluid, and wherein at least one scattered wave propagates through the reaction fluid.

8 (Currently amended). [[A]] The system according to claim 7, wherein the detector is positioned outside the reaction vessel.

9 (Currently amended). [[A]] The system according to claim 8, wherein the reaction vessel is shaped relative to the position of the carrier surface and the position of the detector so as to minimise the effect of fluctuation in the refractive index of the reaction fluid on the interference detected by the detector.

10 (Currently amended). [[A]] The system according to ~~any preceding~~ claim 1, wherein the SEW is a surface plasmon.

11 (Currently amended). [[A]] The system according to ~~any preceding~~ claim 1, further comprising a polymerase on the carrier surface suitable for matching complimentary base pairs of a DNA strand, wherein the system is used to monitor a DNA sequencing operation.

12 (Currently amended). [[A]] The system according to ~~any preceding~~ claim 1, wherein a plurality of areas of the carrier surface can be monitored simultaneously, and/or sequentially.

13 (Cancelled).

14 (Currently amended). [[A]] The system according to claim 12 [[or 13]], wherein the carrier surface includes a plurality of structures of different width.

15 (Original). A carrier chip for a specimen to be monitored, comprising:
a dielectric substrate; and
a conductive film formed on the surface of the substrate suitable for carrying the specimen;

wherein the conductive film comprises first means for splitting an incident wave into a first scattered wave and a surface electromagnetic wave (SEW), the SEW propagating along the carrier surface and interacting with the specimen, and a second means for generating a second scattered wave from the SEW.

16 (Currently amended). [[A]] The carrier surface according to claim 15, wherein at least one of the first and second means ~~are discontinuities~~ is a discontinuity in the conductive film.

17 (Cancelled).

18 (Currently amended). ~~[[A]]~~ The carrier surface according to claim 16, wherein the discontinuity is a discontinuity in the refractive index of the carrier surface or adjacent materials.

19 (Currently amended). ~~[[A]]~~ The carrier surface according to ~~any one of claims~~ claim 15 ~~[[to 18]]~~, further comprising means for generating a reference scattered wave.

20 (Currently amended). ~~[[A]]~~ The carrier surface according to claim 19, wherein the reference scattered wave is generated from an incident wave.

21 (Currently amended). ~~[[A]]~~ The carrier surface according to claim 19 ~~[[or 20]]~~, wherein the reference scattered wave interferes with both the first or second scattered wave at a different spatial frequency from that at which the first and second scattered waves interfere.

22 (Currently amended). ~~[[A]]~~ The carrier surface according to ~~any one of claims~~ claim 15 ~~[[to 21]]~~, wherein the second means is an increase in the thickness of the film in the direction of propagation of the SEW.

23 (Original). A method of monitoring a specimen undergoing a physical, chemical or biochemical reaction occurring on a surface supporting surface electromagnetic waves (SEW), comprising the steps of:

splitting an incident wave into a first scattered wave and SEW such that the SEW propagates along the surface and interacts with the specimen;

splitting the SEW which has interacted with the specimen to generate a second scattered wave; and,

monitoring the interference pattern between the first and second scattered waves.

24 (Currently amended). [[A]] The method according to claim 23, wherein the incident wave is a SEW.

25 (Currently amended). [[A]] The method according to claim 23 [[or 24]], wherein the incident wave is generated by a coherent light source.

26 (Currently amended). [[A]] The method according to ~~any one of claims~~ claim 23 [[to 25]], wherein the specimen is held within a reaction fluid in a reaction vessel, and at least one of the first and second scattered waves propagates through the reaction fluid.

27 (Currently amended). [[A]] The method according to claim 26, wherein the monitoring of the interference pattern takes place outside of the reaction vessel.

28 (Currently amended). [[A]] The method according to claim 27, wherein the reaction vessel is shaped so as to minimise the effect of fluctuations in the refractive index of the reaction fluid on the interference pattern between the first and second scattered waves.

as shown in Figure 2.

Below it will be shown that for any particular interference minimum number m there is such tilted angle φ that at any variations of the RI of the liquid the position of the minimum m on the 2-section photodiode practically will not be changed (but will have the same "interferometric" sensitivity to the variation of wavevector k_{SP} of the SP). This second improvement factor (SIF) depends on the value of the deviation of the RI from the preliminary selected set point (the suppression of the small deviations is more intensive). As it will be shown, in the case of the deviation from 1.327 to 1.33 (this corresponds to water heating by 30°C) the SIF is about 100. In the case of the deviation from 1.3270 to 1.3273 (this corresponds to water heating by 3°C) the SIF is about 10000.

The total improvement factor (TIF) is $TIF = FIF \times SIF$.

An added advantage of the presented interferometric scheme should also be pointed: it is absence of the vibrational noise (without complicated "holographic" vibrational stabilization), since the path difference a does not suffer from the vibrational noise.

The mathematical foundations of our claims is as follows:

Since dimension of the film a is much more less than dimensions $b + c$ (see Figure 2) the path difference between the interfering waves and the condition for an interference extremum may be found from ABD triangle and have the form:

$$a(n_{SP} - n \cos(\theta)) = (m + \Delta m)\lambda. \quad (1)$$

Here m is the number of the extremum, which is an integer for a maximum and a half integer for a minimum, Δm is the total additional phase shift between the interfering waves appearing upon the excitation and detachment of the SEW, λ is wavelength of the light and

$$n_{SP} = \sqrt{\frac{\epsilon_M n^2}{\epsilon_M + n^2}} \quad (2)$$

is the "refraction index" of the SP. In approximations $-\epsilon_M \gg n^2$ and $\theta \ll 1$ equation (1) has the form

$$an \left(\frac{n^2}{2|\epsilon_M|} + \frac{\theta^2}{2} \right) \simeq (m + \Delta m)\lambda. \quad (3)$$

Since we have sum of two positive value in the bracket we cannot make the path difference between the interfering waves precisely equal to zero in this geometry (i.e. work with $(m + \Delta m) \equiv 0$) and cannot obtain perfect compensation ($FIF \rightarrow \infty$).

The angle of a maximum of a diffraction is $\theta_{max} = \pi/2 - \arccos(Z) \approx n/(|\varepsilon_M|)^{1/2}$ (Konopsky, Alieva. Journal of Modern Optics, 2001; 48(10):1597-1615), and therefore the next rough estimation may be done:

$$an \left(\frac{n^2}{|\varepsilon_M|} \right) \simeq (m + \Delta m)\lambda . \quad (4)$$

Therefore, in this case, the situation is $|\varepsilon_M|/n^2$ -times better then in ordinary SPR schemes, where temperature and other variations affect on total optical length an (in our case only path with dimension in several wavelengths $[(m + \Delta m)\lambda]$ undergo such variations). It is the mathematical foundation for FIF.

The mathematical foundation for SIF is next:

The angle θ , which determinate the direction on the extremum m may be derived from (1):

$$\theta = \arccos \left(\frac{n_{SP}}{n} - \frac{(m + \Delta m)\lambda}{an} \right) \quad (5)$$

(note that this angle depends on n and it decreases when n increases). But angle θ' (see Figure 2) is associated with θ by Snell's law:

$$n \sin(\theta + \varphi) = \sin(\theta' + \varphi) , \quad (6)$$

where φ is the tilted angle of the cell's wall. One can see that according to (6) θ' is increases when n increases.

Therefore there is such an angle φ that variations in n will be not reflected in θ' .

This angle may be found by solving equations

$$\frac{\partial}{\partial n} (n \sin(\theta + \varphi)) = 0 , \quad (7)$$

in respect of φ .

The solution is

$$\varphi_0 = \arctan \left(\frac{(m + \Delta m)\lambda - an_{SP}^3/\varepsilon_M}{\sqrt{a^2 n^2 - (an_{SP} - (m + \Delta m)\lambda)^2}} \right) - \arccos \left(\frac{an_{SP} - (m + \Delta m)\lambda}{an} \right) . \quad (8)$$

At such tilted angle φ a small variation in n will not change the direction θ' on the extremum number m .

But the sensitivity to the variations of k_{SP} will be the same; because, in this case, only the angle θ will change (without simultaneous changes of the n of the liquid).

The expression taken into account the finite dimensions of b and c is more complicated than (8), but also may be obtained (in this case φ should be $> \varphi_0$).

Variations of the z -position of the interference minimum with number m are shown on the Figure 3 (in this example we take $m = 4, a = 100 \mu\text{m}, \lambda = 1.06 \mu\text{m}, \varepsilon = -60, \varphi = 0.155, b = 10000 \mu\text{m}, c = 20b$). One can see that at RI variations from 1.324 to 1.33 the variations in z -position of the extremum not exceed $\Delta H \simeq 1 \mu\text{m}$.

When the cell's wall is not tilted ($\varphi = 0$), or φ far from φ_0 the variations in z -position of the extremum exceed $100 \mu\text{m}$ at the same RI variations. Therefore the SIF ~ 100 in this case. At smaller RI variations the SIF is increased due to quadratic dependence of $H(n)$ near selected n (see Figure 3).

It may be noted that TIF may be directly obtained by comparison of the value ΔH with interference fringes dimension Λ at the plane of the detection. This value is:

$$\begin{aligned} \Lambda &= 2\pi/(2k \sin(\partial\theta'/2)) \simeq 2\pi/(k\partial\theta') = 2\pi/(nk\partial\theta) \\ &= \lambda/(n\partial\theta) \simeq \lambda(H^2 + (b+c)^2)^{1/2}/(an \tan(\theta)) \approx 14000 \mu\text{m}. \end{aligned} \quad (9)$$

In ordinary interferometric scheme phase shift due to RI variations is $a\Delta n$. TIF may be obtained from the next equation:

$$\frac{\Delta H}{\Lambda} = \frac{1}{\text{TIF}} \frac{a\Delta n}{\lambda}. \quad (10)$$

This estimation gives the same TIF value as FIF \times SIF.

It should be noted that the method of "tilted cell's wall" may be also used in an ordinary prism-based Kretschmann configuration, which employs the angular interrogation, if prism is entirely immersed in the liquid, and output cell's wall is tilted at appropriate angle. In this case only SIF will be used (subject to conditions that RI variations of the liquid are the same under a metal film and near the cell's wall).